



1-Methoxy, 2-Amino, 4-Acetophenone and Its Derivatives. Relation Between Molecular Structure and Odor in Tri-Substituted Benzenes

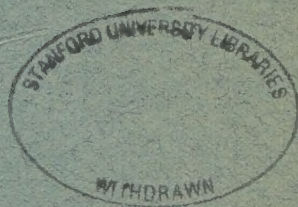
DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN
THE FACULTY OF PURE SCIENCE OF
COLUMBIA UNIVERSITY

BY

LEO P. CURTIN, A.B., A.M.

NEW YORK CITY
1923



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Dissertation

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TO MAY FRANCES CURTIN, MY WIFE,
THIS RESEARCH IS AFFECTIONATELY DEDICATED

ACKNOWLEDGMENT

This work was suggested and directed throughout by Professor Marston Taylor Bogert. Its completion would have been impossible without his invaluable criticism and advice. For this, and for his unvarying attitude of kindness and courtesy, the author wishes to express his appreciation and thanks.

1-Methoxy, 2-Amino, 4-Acetophenone and Its Derivatives. Relation Between Molecular Structure and Odor In Tri-Substituted Benzenes

ABSTRACT OF DISSERTATION

For what reason was the research undertaken?

The research was undertaken for the purpose of studying the relation between structure and odor in certain derivatives of para-methoxy acetophenone, a substance which itself has a fine floral odor. It is known that derivatives which have the substituting group ortho to the aceto and meta to the methoxy are likely to be odorous. In particular, 1-methoxy 3-hydroxy 4-acetophenone (paeonol), has a flowerlike odor and is used in the perfume industry. It was desired to ascertain what would be the effect on odor if the substituting group were put in the other position.

What was the method of attack?

Starting with 1-methoxy 4-acetophenone, various 1, 2, 4, derivatives were prepared and the influence of the new group on the odor was noted. Some of the substituting groups were themselves osmophores.

To what extent successful?

A number of 1, 2, 4 derivatives were prepared and studied and the information thus obtained was correlated with previously existing knowledge on the subject.

What contributions new to the science of chemistry have been made?

- a—A number of new compounds have been prepared and a suitable synthesis given for each. (A full list is given in the discussion.)
- b—All of the 1,2,4 derivatives of 1-methoxy 4-acetophenone which were prepared were found to be odorless, even when the group in the 2 position was itself an osmophore.
- c—The following propositions relating to steric hindrance are advanced:
 - 1—The hindering effect of the group causing steric hindrance increases as the molecular weight of the group increases;*
 - 2—The hindering effect of a given group diminishes as the molecular weight of the reacting group in the ortho position increases;

* V. Meyer, *Berichte*, **28**, 1260 (1895).

3—The hindering effect of a given group diminishes as the molecular weight of the foreign, reacting molecule increases.

The first has already appeared in the literature in a different form.* The second and third were suggested by difficulties encountered in the present research. Based on these theories, suggestions are made (1) about predicting, in certain cases, the probable outcome of untried reactions and (2) about facilitating certain reactions which are unsatisfactory because of steric hindrance.

INTRODUCTION

The question of the relation of odor to molecular structure is one about which little is known. While considerable empirical knowledge is available, we usually are not able to predict, from its structural formula, whether or not a new compound having osmophore groups will have an odor. To describe in advance the nature of the odor the new compound will have, is, of course, still more difficult.

On the other hand, the relation between structure and color has been investigated in great detail and much of value has been discovered. From its structural formula, one usually can foretell, in a general way, what will be the color of a new compound containing chromophore groups and how the color will be altered by the introduction of substituting groups in the various positions.

The color industry is of vastly greater commercial importance than the perfume industry and this condition is mainly responsible for the disparity in the scientific development of the two fields.

Investigators in perfume chemistry are hampered by the fact that there are no known physical constants, as wave lengths in color investigations, to guide them. The color chemists are helped in that the mechanism of sight is at least partly understood while, in the odor field, the nature of the phenomenon of smelling is still open to the wildest speculation.

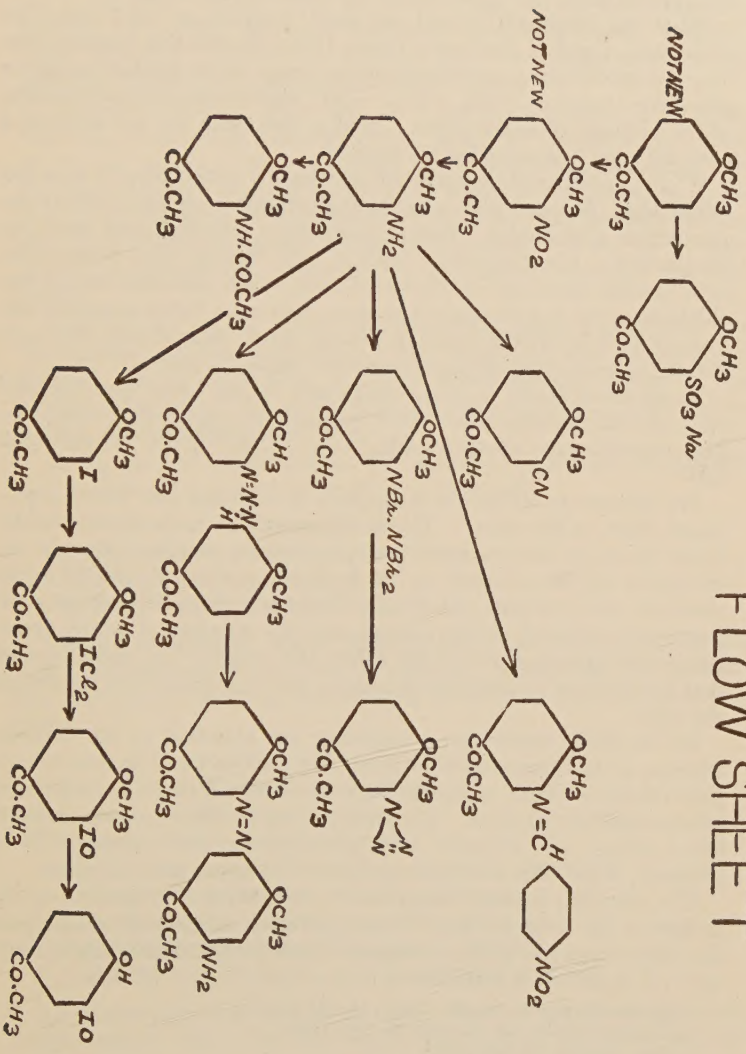
Although subordinate commercially, odor chemistry is as important as color chemistry from a scientific point of view and will sometime be as thoroughly investigated.

DISCUSSION

While the investigation of the relation of odor to structure has not made great progress, many important facts have been recorded and numerous rules formulated, holding, however, only within narrow limits. Following are the more important data pertinent to this discussion.

It was long since observed that, usually, there was found one or more of a small class of organic radicals in substances which possessed a fine odor. The radicals or groups most frequently encountered in perfumes were $-\text{OH}$, $-\text{O}-$, $-\text{NO}_2$, $-\text{N}_3$, $-\text{CHO}$, $-\text{COR}$, $-\text{CH}_3$, $-\text{OCH}_3$,

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$-\text{CN}$ and $-\text{C}\equiv\text{C}-$. A carbon atom loaded up with alkyl groups, as isopropyl in para-cymene derivatives,¹ ionone² and tertiary butyl in the various musk perfumes,³ is also an odor-bearing group.

Rupe and Majewski⁴ coined the word "osmophore" as a name for these groups and, a year later, Georg Cohn divided this classification into two subdivisions, cacosmophores or groups which produce offensive odors, as $-\text{C}\equiv\text{C}-$, $-\text{SH}$, $-\text{S}-$, $-\text{NC}$, and euosmophores or groups which produce pleasant odors. In this discussion we are concerned only with the last named subdivision.

While a substituted hydrocarbon may have a certain odor, it does not follow that the particular substituting osmophore is essential to the production of that odor. Benzaldehyde has a bitter-almond odor, yet nitrobenzene, nitrothiophene, methyl tolyl ketone and benzonitrile have similar odors and hydrocyanic acid, which contains neither the aldehyde group nor the phenyl nucleus, also has a bitter-almond odor. From this it is evident that, in certain cases, osmophores may substitute for each other without important change in odor.⁵

There are a dozen or more compounds which have bitter-almond odors and large groups which have, respectively, pepper-like, camphor-like, anise-like and cinnamon-like odors. Cohn⁶ gives several such lists.

The nucleus to which the osmophore is attached also exerts a profound effect on the odor.⁵ This is demonstrated in the series of aldehydes where we have a great variety of odors, ranging from the unendurable acrylic aldehyde to the floral odors of citral, phenyl acetic aldehyde and cinnamic aldehyde. Prins⁷ regards each odorous compound as composed of two osmophores, the stronger of which determines the type of odor and the other, the variety. It might be said that the stronger determines the genus, and the weaker the species, of the odor.

In the cases where two osmophores are attached to the benzene nucleus, if the compound is odorous, they will be found in the ortho or para relation. Meta compounds are, in nearly all cases, of very slight odor or entirely odorless. For instance, ortho-methoxy acetophenone has a strong, very offensive odor, para-methoxy aceto-phenone has a pleasant, floral odor and meta-methoxy acetophenone is odorless.

The situation is more complicated when three osmophores are attached to the benzene ring. Nearly all such compounds which have fine odors have two of the osmophores para to each other, that is, they are 1, 2, 4, or 1, 3, 4 derivatives.

¹ Gertrud Woker, *J. Physical Chem.*, **10**, 455 (1906).

² Tiemann and Kruger, *Berichte*, **26**, 2691 (1893).

³ Baur, *Berichte*, **30**, 303 (1897).

⁴ Rupe and Majewski, *Berichte*, **33**, 3402 (1900).

⁵ Delange, *Bull. de la Société Chimique de France*, (Feb., 1922).

⁶ Cohn, *Die Riechstoffe*, 1904.

⁷ Prins, *Perfum and Essential Oil Record*, 222 (July, 1917).

Georg Cohn calls this grouping in all types of six-membered cycles the "ideal configuration" for the production of perfume substances and cites numerous odorous compounds, the structures of which bear out his theory. Among them are borneol, menthol, carvone, fenchone, thujone, menthone, pulegone, camphor, carvacrol, thymol, eugenol, safrol, piperonal, vanillin and acetovanillin. Noelting's work on the artificial musks⁸ also substantiates Cohn's theory.

Another compound which has the ideal configuration is paeonol, 1-methoxy 3-hydroxy 4-acetophenone, found in Nature in the roots of *paeonia moutan*. Since paeonol has a fine, flowerlike odor, the question naturally suggests itself—what would be the properties with respect to odor of the 1,2,4, derivatives of 1-methoxy 4-acetophenone, since they would also have the ideal configuration? It was for the purpose of answering this question that the present research was conducted.

Starting with anisole, para-methoxy acetophenone was prepared by the Friedel and Craft's reaction. This compound was nitrated and reduced, giving 1-methoxy 2-amino 4-acetophenone. This is the parent substance of the new compounds here described, with the exception of the sodium sulphonate.

An improved synthesis is given for 1-methoxy 2-nitro 4-acetophenone and the following new compounds were prepared:

- 1-methoxy 2-amino 4-acetophenone;
- 1-methoxy 2-cyano 4-acetophenone;
- 1-methoxy 2-iodo 4-acetophenone;
- 1-methoxy 2-azido 4-acetophenone.

The five compounds above named carry three osmophores in the 1, 2, 4 positions and all proved to be odorless. In addition, the following new compounds carrying non-osmophores in the 2 position were prepared:

- 1-methoxy 2-acetamido 4-acetophenone;
- 1-methoxy 2-dichloriodo 4-acetophenone;
- 1-methoxy 2-iodoso 4-acetophenone;
- 1-hydroxy 2-iodoso 4-acetophenone;
- 1-methoxy 2-(para-nitrobenzalimino) 4-acetophenone;
- 2-methoxy 5-aceto benzene sodium sulphonate;
- 2-methoxy 5-aceto diazobenzene perbromide;
- 2,2'-dimethoxy 5,5'-diaceto diazoamino benzene;
- 2,2'-dimethoxy 5,5'-diaceto para-aminoazo benzene.

These also proved to be without odor. Some of the second group are compounds of high molecular weight and their lack of odor was not unexpected.

⁸ Noelting, *Chimie et Industrie*, 6, 719 (1921).

Attempts to synthesize the following named compounds were, for various reasons, unsuccessful:

- 1-methoxy 2-hydroxy 4-acetophenone;
- 1-hydroxy 3-methoxy 4-amino 6-acetophenone;
- 2-methoxy 5-aceto benzoic acid;
- 2-methoxy 5-aceto benzamide;
- 2-methoxy 5-aceto methylimino benzoic ester;
- 2-methoxy 5-aceto phenyl hydrazine hydrochloride;
- 5-aceto 8-methoxy quinoline;
- 2,2'-dimethoxy 5,5'-diaceto hydrazobenzene.

It is evident that the conditions necessary to produce odor in trisubstituted benzenes are exceedingly complex and poorly understood. It will be necessary to make hundreds of new trisubstituted benzenes before sufficient information is available from which to induce laws applicable to this class of compounds.

The hydroxy methoxy aldehydes and ketones probably have been more thoroughly investigated than any others in the trisubstituted class, yet in both cases less than half of the ten possible isomers have been prepared. The work done on trisubstituted compounds containing the azido group, the nitro group and the cyano group is almost negligible.

At present, the best we have is Cohn's rule, previously referred to, which, stated in different language says that, in six-membered cycles containing three osmophores, two of them must be in the para relation. If this condition is satisfied, the compound *may* be odorous; if not, it will almost certainly be odorless.

While para-methoxy acetophenone itself is very stable and can be distilled at 258° without decomposition, its derivatives are rather unstable to heat, particularly in the presence of acid or alkali. In the preparation of most of them, considerable amounts of tarry substances appeared as by-products.

In several cases, considerable difficulty was experienced in bringing about reactions involving the group ortho to the methoxy group. The methoxy group is well known to students of steric hindrance and has figured extensively in the literature on that subject. Many reactions which proceed smoothly in ordinary cases take place with difficulty, or not at all, when methoxy is adjacent. For instance, the conversion of aniline to phenol by diazotization and hydrolysis is accomplished readily at temperatures much below the boiling point. The conversion of ortho-anisidine to guaiacol by the same method, however, is rather difficult. Methods for bringing it about have been the subjects of numerous patents.

In this research, it was found impossible to hydrolyze the cyano compound to the amide, to the acid or to the methyl imido ester. The

amino compound could not be converted into the corresponding phenol by any method tried.

When these difficulties were encountered, some consideration was given to the question of steric hindrance, particularly with respect to the reactions used in this research.

It is generally understood that the spatial configurations of the groups involved are factors in determining the degree of steric hindrance. Furthermore, reactivity may be increased or decreased by loading up a nucleus with positive or with negative groups. For example, acid groups in the ortho position increase the rate of hydrolysis of an ester, while methyl groups in the ortho position retard it.

In addition to the foregoing, the following propositions are now advanced, the first of which has already appeared in the literature:

- 1—The hindering effect of the group causing steric hindrance increases as the molecular weight of the group increases;⁹
- 2—The hindering effect of a given group diminishes as the molecular weight of the reacting group in the ortho position increases;
- 3—The hindering effect of a given group diminishes as the molecular weight of the foreign, reacting molecule increases.

These propositions are, of course, of a qualitative nature. Numerous contradictions can be found, as is usually the case with theories concerning organic chemistry. They are based on simple, physical considerations of mass and inertia and, in this respect, have the advantage of more far-fetched theories.

They are advanced in the hope that they will enable investigators to predict, in certain cases, the probable outcome of untried reactions and, also, that they will suggest a means of improving reactions which work poorly, or not at all. For example, if a Sandmeyer reaction were unsuccessful with potassium cuprocyanide, it might succeed with potassium argenticyanide, a somewhat heavier molecule.

An excellent illustration is found in the preparation of mesitylene carboxylic ester. Victor Meyer¹⁰ could not prepare this substance, which has two methyl groups ortho to the carboxyl, by passing HCl into the acid and methyl alcohol. (Methyl benzoate is formed in almost quantitative yield by a similar reaction.) By using the silver salt of the acid, (Proposition 2), and methyl iodide in place of methyl alcohol. (Proposition 3), the ester is readily prepared.

In the following table, Kellas¹¹ shows how ortho substituting groups affect the rate of hydrolysis of esters, (Prop. 1):

Group ortho to COOR.....	CH ₃	Cl	Br	I	NO ₂
M. W. of group.....	15	35	80	127	46
% yield, 2 hrs. 51°.....	48.3	50.9	34	20.5	8.6

⁹ V. Meyer, *Berichte*, **23**, 1260 (1895).

¹⁰ V. Meyer, *Berichte*, **27**, 510 (1894).

¹¹ Kellas, *Zeit. Phys. Chem.*, **24**, 221 (1897).

In the aliphatic series, Sudborough¹² shows how substituting groups affect the rate of formation of esters, (Prop. 1).

Acid	Esterification Const.	M. W. Subst. Group
Acetic.....	3.661	1
Methyl acetic.....	3.049	15
Chloracetic.....	2.432	35
Phenylacetic.....	2.068	77
Bromacetic.....	1.994	80
Iodacetic.....	1.713	127
Dimethylacetic.....	1.019	30
Dichloracetic.....	0.064	71
Diphenylacetic.....	0.056	154
Dibromacetic.....	0.051	160

No part of the experimental work of the research is in disagreement with the three propositions. The failures to hydrolyze the cyano compound and the diazonium chloride with water, methyl alcohol and hydrogen peroxide were unsuccessful. In these cases the foreign reacting molecule was not far from the weight of the hindering group, methoxyl.

The reactions involving heavy foreign molecules were particularly satisfactory, notably with KCuCN_2 , HI , Sn , and in the formation of the Schiff's base and the diazoamino compound.

A rather striking confirmation of Proposition 2 is found in the formation of the azido compound by treating the diazoperbromide with ammonia. Here the foreign reacting molecule has a M. W. of but 17. The diazoperbromide group, however, has a M. W. of 268 and the methoxy group, M. W. 31, is not able to prevent the instantaneous formation of the azido compound.

EXPERIMENTAL PART

Para-methoxy acetophenone.—This compound has been prepared by several investigators, notably Gattermann, Ehrhardt and Maisch,¹⁴ and Charon and Zamanos.¹³ The Friedel and Crafts reaction was generally employed and, in most cases, gave inferior yields. Of the several methods which were tested in these experiments, the most successful is described below.

This compound is prepared by the interaction of anisole and acetyl chloride in the presence of aluminum chloride, using carbon disulphide as solvent and diluent. Apparatus for the Friedel and Crafts reaction is equipped with an automatic stirrer and the reaction flask imbedded in an ice-pack. Slightly more than the calculated quantity of AlCl_3 is placed in the flask, then the CS_2 is added. The anisole is then al-

¹² Sudborough, *Trans. Chem. Soc.*, **75**, 467 (1899).

¹³ Gattermann, Ehrhardt and Maisch, *Berichte*, **23**, 1201 (1890).

¹⁴ Charon et Zamanos, *Comptes Rendus*, **133**, 741 (1900).

lowed to flow in slowly, with stirring. If the reaction mixture is not kept well cooled at this time, a high yield of tarry products will be obtained. The amount of anisole used serves as a basis for computing the quantities of other reagents. Slightly more than the calculated quantity of acetyl chloride is then added slowly from a dropping funnel, keeping the temperature below 10° and taking two hours for the operation.

The reaction mixture is finally heated for two hours on the steam bath, then the CS₂ is driven off and the addition compound decomposed by pouring upon cracked ice. The ketone and other organic substances are extracted with ether, the ether driven off and twice its volume of cold alcohol added to the residue. Upon stirring, unsymmetrical *p-p*-dimethoxy diphenyl ethylene remains undissolved and is filtered out. This substance is purified by crystallization from boiling alcohol. Beautiful, colorless leaflets; m. p., 140° uncorr. Gattermann¹⁵ also reports a m. p. of 140° uncorr. on this substance.

After driving off the alcohol, the residue is distilled at atmospheric pressure, the fraction coming over between 250° and 275° containing the desired ketone. It is slightly volatile with steam and may be distilled by this method with a small increase in yield.

The distillate solidifies on cooling and may be separated from the small amount of non-crystallizing oil which is present by filtering with suction, then pressing out on a porous plate. Para-methoxy acetophenone, very large, colorless rhomboid tables from ether; m. p., 38–39° uncorr.; b. p., 258° uncorr. These constants exactly check those reported by Gattermann Ehrhardt und Maisch (loc. cit.).

Yield, with steam distillation, 61 per cent of theory. Using the same method but with petroleum ether as solvent, the yield was 8 per cent. Using an excess of anisole as solvent, the yield was 30 per cent.

The method of adding the acetyl chloride is due to Charon and Zamanos and results in a considerably increased yield. They claim to get a theoretical yield by this means. It is difficult to understand how this is possible. An abundant yield of tarry substances is obtained, five to ten per cent of the anisole goes to form the substituted ethylene previously described, and beta-diketones, from a side reaction of the acetyl chloride, were observed.

The remainder of the procedure outlined above is due to Gattermann, Ehrhardt and Maisch. They do not publish the yield obtained but, otherwise, their results were duplicated in these experiments.

1-Methoxy 2-nitro 4-acetophenone—This compound was prepared by Stockhausen and Gattermann,¹⁶ while studying the Friedel and Crafts reaction, the method used being the acetylation of *o*-nitro anisole with acetyl chloride in the presence of aluminum chloride. The yield was poor, less than nine per cent, as was to be expected from the presence

¹⁵ Gattermann, *Berichte*, **22**, 1132 (1889)

¹⁶ *Berichte*, **25**, 3521 (1892).

of the strongly acid nitro group already in the nucleus. An excellent yield of this compound may be obtained by the following procedure:

Fifty grams p-methoxy acetophenone is dissolved in 200 cc. conc. H_2SO_4 at room temperature. Conc. nitric acid containing one-third mole HNO_3 is mixed with an equal volume of conc. H_2SO_4 and cooled to a low temperature.

The dissolved p-methoxy acetophenone is cooled in an ice-saltwater bath to 0° with the help of an automatic stirrer, then the nitrating mixture is allowed to drop in slowly. One hour is consumed in adding the nitrating mixture. Stirring is continued for fifteen minutes longer, then the mixture is poured into a liter of ice-water. The nitro ketone separates as a light-yellow, flocculent precipitate. After standing for one hour, it is filtered out with suction, dried and recrystallized from alcohol.

1-Methoxy 2-nitro 4-acetophenone, slender, lemon-yellow needles from alcohol; m. p., 99.5° corr. Stockhausen und Gattermann, (loc. cit.), report m. p., 99.5° uncorr. Yield, 95 per cent of theory. The yield was determined after one crystallization from alcohol.

1-Methoxy 2-amino 4-acetophenone—This substance was prepared by reduction of the corresponding nitro compound. 300 cc. conc. HCl and 150 gm. granulated tin are placed in a liter beaker and 65 gm. nitro compound is added in small portions. The reaction mixture soon becomes hot and the nitro compound is added at a rate just sufficient to maintain the temperature at the boiling point. After all has been added, the mixture is heated for one hour on the water bath, then filtered hot to remove tin and other solid matter. The filtrate is cooled, diluted to a volume of one liter and made strongly alkaline. The impure amino compound, accompanied by considerable tin oxides, is filtered out with suction, using a cotton cloth filter, and the filtrate is discarded. The precipitate is brought into solution by heating with a slight excess of dilute HCl , heated with boneblack for several hours, filtered and the filtrate made strongly alkaline as before. The precipitate is filtered out, washed, dried and recrystallized from alcohol. Yield, 74 per cent of theory.

The precipitate from the second alkaline solution contains a small amount of tin. This should be extracted several times with hot alcohol to avoid losing product.

The amino compound as obtained from the first alcoholic crystallization is light yellow in color. A further treatment with boneblack and two or three additional recrystallizations will give a perfectly white product.

1-Methoxy 2-amino 4-acetophenone, large, flat colorless hexagonal prisms from alcohol; m. p., 102.0° corr.; easily soluble in benzene; moderately soluble in ether.

Analysis: $C_9H_{11}O_2N$	Calc.	Found
C	65.45	65.68
H	6.67	6.77

1-Methoxy 2-acetamido 4-acetophenone—This compound is formed by dissolving the corresponding amine in a small excess of acetic anhydride and allowing to stand for two or three days. The anilide crystallizes from the solution in four sided prisms of rhombical cross-section, colorless, m. p., 122.5° corr.

Recrystallization of the anilide from hot water is not satisfactory. While it is soluble in hot water, it is so readily hydrolyzed that the fine white needles formed on cooling are contaminated with sufficient amine to lower the melting point several degrees. It may be crystallized from acetic acid, in which it is very soluble.

Analysis: $C_{11}H_{13}O_3N$	Calc.	Found
C	63.75	63.68
H	6.33	6.25

Attempted synthesis of 1-methoxy 2-hydroxy 4-acetophenone—Of the two possible nuclear monohydroxy derivatives of p-methoxy acetophenone, but one is known. This is paeonol, a sweet smelling substance, found in the roots of *paeonia moutan*. In attempting the preparation of the remaining isomer, isoacetovanillone, the following methods were tried.

1—Fusion of 1-methoxy 4-aceto 6-benzene sodium sulphonate with a low melting mixture of NaOH and KOH. Although the fusion lasted but three minutes, the molecule was completely destroyed. An insignificant amount of phenolic substances was recovered. This proved to be mainly derivatives of catechol which showed that the fusion had, among other effects, disrupted the ether linkage. With ferric chloride, an instant deep green color was obtained, becoming dark red upon addition of sodium carbonate.

2—Diazotization of the corresponding amine and hydrolysis by simply heating the aqueous solution; hydrolysis by dropping the cold diazonium sulphate solution into a mixture of H_2SO_4 and $NaHSO_4$ at $140^\circ C.$; adding the cold solution to a boiling mixture of equal weights of $CuSO_4$ and water. No isoacetovanillone was obtained in any case; tarry substances were the sole products. The last two methods are patented for the production of guaiacol from o-anisidine.

Since the above work was done, Schneider and Kraft¹⁷ have published an account of the synthesis of isoaceto-vanillone by condensing guaiacol with sulfoacetic acid.

1-Methoxy 2-cyano 4-acetophenone—This compound was prepared by the Sandmeyer reaction, starting with 1-methoxy 2-amino 4-acetophenone.

¹⁷ Schneider and Kraft, *Berichte*, **55B**, 1892 (1922).

The cold diazonium chloride is added to a potassium cuprocyanide solution at 80° C. The nitrile is precipitated at once as light-brown particles. The precipitate is dissolved in boiling alcohol, treated with boneblack and filtered at the boiling temperature.

1-Methoxy 2-cyano 4-acetophenone, fine, pale-yellow needles from alcohol which soon assume a light orange-yellow color; m. p., 159.5° corr., yield 70 per cent of theoretical. Moderately soluble in ether and alcohol, very soluble in benzene.

Analysis: $C_{10}H_9O_2N$	Calc.	Found
C	68.55	68.35
H	5.18	5.27

Attempted synthesis of 2-methoxy 5-aceto benzoic acid—The following methods were tried: (a) heating with 70 per cent H_2SO_4 for several hours; (b) heating with 5M. KOH for several hours; (c) boiling with conc. HCl for ten hours; (d) fusing the sodium sulphonate described below with sodium formate. All were unsuccessful. In (a) and (b), tarry products were obtained; in (c), a black powder resembling charcoal was the sole product; in (d), the fusion destroyed the molecule, as in the attempt to make the phenol. Several attempts were made by method (a) and from these a few milligrams of a carboxylic acid were collected. This impure substance melted at 255° with decomposition.

Attempted synthesis of 2-methoxy 5-aceto benzamide—The corresponding nitrile was treated with alkaline hydrogen peroxide and held at 40° for thirty minutes.¹⁸ No hydrolysis took place at this temperature or higher and the nitrile was recovered unchanged.

Attempted synthesis of the methyl imino ester of 2-methoxy 5-aceto benzoic acid—The imino ester, if formed, would be a convenient source for the preparation of the corresponding oxygen ester and the carboxylic acid. The method used was that of Pinner,¹⁹ in which anhydrous methyl alcohol and a nitrile are condensed by passing in dry HCl. Although the HCl was passed in for several hours, the reaction was a complete failure; no trace of imino ester hydrochloride was formed and the nitrile was recovered unchanged.

1-Methoxy 2-iodo 4-acetophenone—A solution of potassium iodide is added to an ice-cold solution of the proper diazonium chloride and allowed to stand for three hours, then heated on the steam bath for thirty minutes. After cooling, the impure iodo compound is filtered out and recrystallized two or three times from fifty per cent acetic acid. Most of the tarry products can be separated from the hot solution by decantation. Very soluble in alcohol, chloroform, ether and acetic acid. Yellow, feathery needles which quickly turn light-brown, from dilute acetic acid, m. p., 103.6° corr.; yield, 55 per cent.

¹⁸ Radziszewski, *Berichte*, **18**, 355 (1885).

¹⁹ Pinner, *die Imidoäther und ihre Derivate*, **1892**.

Analysis: $C_8H_5O_2I$	Calc.	Found
C	39.13	39.29
H	3.26	3.36

1-Methoxy 2-dichloriodo 4-acetophenone—Prepared by passing dry chlorine into a chloroform solution of the iodo compound. It is impossible to prepare a pure sample of the substance as it commences to give off chlorine when free from the chloroform. If kept for a time in a tightly stoppered bottle, the chlorine liberated substitutes for hydrogen in the molecule and the only gas remaining is HCl. As this substitution apparently gave a mixture of products, it is probable that chlorine substituted in the nucleus para to the iodo and also substituted for part of the hydrogen in the aceto group. Fine, bright-yellow crystals; no definite melting point.

1-Methoxy 2-iodoso 4-acetophenone—This substance was made by triturating freshly prepared dichlor-iodo compound with 5 molar KOH. It is a dirty-white, puttylike, amorphous mass, decomposing suddenly when heated. Attempts to purify by crystallization were unsuccessful; while soluble in alcohol and other solvents, it was reprecipitated in a slimy, amorphous form.

1-Hydroxy 2-iodoso 4-acetophenone—In the preparation of the methoxy iodoso compound above described, the clear, alkaline filtrate was acidified by passing in SO_2 and a precipitate separated. This was at first thought to be a substituted iodonium iodide, as this is one method of preparation.²⁰

It was observed to be easily soluble in dilute alkali, which is not a property of iodonium iodides, and the analysis gave too low a carbon content for the iodonium compound. The fact that the compound could be precipitated from its alkaline solution with sulphurous acid or acetic acid indicated a free phenolic hydroxyl group. It seemed probable that the strong alkali used in hydrolyzing the dichloriodo compound had also hydrolyzed the methyl ether linkage. While structurally an ether, the presence of acid groups in the ortho and para positions had given the compound the chemical properties of an ester, as with the poly-nitro phenols.

Long, pale-yellow needles from fifty per cent alcohol; no color with ferric chloride; decomposes suddenly when heated rapidly; easily soluble in alcohol and benzene, moderately soluble in ether; m. p., with decomposition, 243° corr.

Analysis: $C_8H_7O_2I$	Calc.	Found	Found
C	34.55	33.58	34.28
H	2.54	2.62	2.68

2-Methoxy 5-aceto benzene sodium sulphonate—This compound was prepared in the hope that it might be a convenient intermediate in the preparation of iso-aceto vanillone and other compounds.

²⁰ V. Meyer, *Berichte*, **27**, 1592 (1894).

Para-methoxy acetophenone is not attacked by 95 per cent sulphuric acid at 80°, and but slightly attacked at room temperature by fuming acid containing 15 per cent SO₃. By the use of stronger acid, in large excess, very satisfactory results can be obtained.

One hundred gm. fuming sulphuric acid containing thirty per cent SO₃ is placed in a beaker provided with split watchglasses and a stirrer and cooled to 5° C. Then 25 gm. p-methoxy acetophenone is added in small amounts during a thirty minute interval. Stirring is continued for thirty minutes longer, then the ice-cold mixture is poured with stirring into five times its volume of saturated ice-cold NaCl solution. The sodium sulphonate starts to separate in a few minutes and, after fifteen minutes stirring, the voluminous precipitate is filtered with suction.

Large, snow-white, fatty leaflets which turn pink if exposed to direct sunlight while moist. The sodium salt is quite soluble in water and the acid exceedingly so. Yield, almost quantitative.

Analysis: C ₉ H ₉ O ₆ SNa	Calc.	Found
S	12.69	12.82

Attempted synthesis of 2,2'-dimethoxy 5,5'-diaceto hydrazobenzene and the isomeric benzidine—While most of the simpler nitro compounds are readily reduced to the hydrazo derivative, those which have a methoxy ortho to the nitro group undergo this reduction with difficulty.

The procedure in this case was that of Starke.²¹ The products were brownish, tarry bodies and no hydrazo compound could be isolated. The reaction products were finally treated with conc. HCl and allowed to stand for a day with the expectation that any hydrazo compound would be converted into the benzidine derivative which could easily be recovered. On making the filtrate alkaline, there was no precipitate except a few particles of zinc hydroxide.

Attempted synthesis of 5-aceto 8-methoxy quinoline—The method used was that of Skraup, except that arsenic acid was substituted for nitrobenzene as the oxidizing agent.²² The final products were tars. While there was sufficient quinoline derivative present to give the mass a faint quinolinic odor, the yield was entirely too small to be isolated.

Attempted synthesis of 2-methoxy 5-aceto phenyl hydrazine hydrochloride—Reduction of the potassium diazonium sulphonate with bisulphite was first tried. Either the diazonium compound or the hydrazine proved to be very unstable to heat and no yield was obtained. The next attempt was reduction of the diazonium chloride with stannous chloride in conc. HCl. A heavy precipitate was obtained which proved to be the double tin salt of the hydrazine hydrochloride. This was insoluble in conc. or dilute HCl and no way of removing the tin in acid solution was found except by precipitating the tin with H₂S. As

²¹ Starke, *Journal für Praktische Chemie*, **59**, 210 (1899).

²² Kneppel, *Berichte*, **29**, 704.

the hydrazine hydrochloride was difficultly soluble, this did not aid in its recovery.

On adding alkali to a suspension of the precipitate obtained in the reduction, the free hydrazine was liberated. As a carbonyl group was also present, a series of immediate intermolecular condensations took place with the final production of tars.

2-Methoxy 5-aceto diazobenzene perbromide—Prepared from the corresponding diazonium chloride by adding the calculated quantity of bromine dissolved in hydrobromic acid. The perbromide is instantly precipitated as fine yellow crystals which filter readily. It decomposed on standing or on heating with alcohol.

Flat, pale yellow needles from cold alcohol; m. p., 68–70° C.; yield, almost quantitative.

2-Methoxy 5-aceto azidobenzene—Ammonia water is added, with good stirring, to a fine suspension of the perbromide in water. The azido compound is precipitated at once as a mahogany-red mass. This is filtered out, dissolved in 95 per cent alcohol, then boiled for thirty minutes with boneblack. The filtrate is diluted with three times its volume of water, heated until solution takes place, then set aside to crystallize.

Long, delicate needles of a peculiar, faint pinkish-buff color which darken on standing; m. p., 87° corr. with decomposition. If heated rapidly, an explosion takes place slightly above the melting point. Extremely soluble in benzene and alcohol, readily soluble in ether. Yield, 75 per cent.

Analysis: $C_9H_9O_2N_3$	Calc.	Found
C	56.53	56.33
H	4.74	4.65

Attempted synthesis of 1-hydroxy 3-methoxy 4-amino 6-acetophenone—Para-amino phenols are prepared from azido compounds by heating them with fifty per cent sulphuric acid.²³

The azido compound described above was heated with twenty-five per cent sulphuric acid for fifteen minutes and completely converted into tar. Reaction was a failure.

2,2'-Dimethoxy 5,5'-diaceto diazoamino benzene—10 Gm. 1-methoxy 2-amino 4-acetophenone is dissolved in 50 cc. water and 20 gm. conc. HCl, cooled, then diazotized with $NaNO_2$, using no excess. 10 Gm. of the same amine is dissolved in 20 cc. water and 6 gm. conc. HCl is added, with stirring. A solution of 35 gm. potassium acetate in sufficient water to dissolve is poured in slowly with good stirring. The diazoamino compound is precipitated at once. It is filtered with suction, thoroughly dried, then dissolved in boiling alcohol. The solution is boiled ten minutes with boneblack, which completely removes all impurities, then filtered at the boiling temperature.

²³ Griess, *Berichte*, **27**, 313 (1894).

The filtrate is cooled sharply, using an ice bath. The diazoamino compound is filtered out without delay, using suction. If the pale yellow solution is allowed to cool slowly, needles up to one millimeter in length will be formed but these will be orange in color, contaminated by the isomeric amino azo compound.

The pure product is small, pale yellow needles, sparingly soluble in boiling alcohol and nearly insoluble in cold alcohol; m. p., 178° corr., yield, 95 per cent of theory.

Analysis: $C_{18}H_{19}O_4N_3$	Calc.	Found
C	63.34	63.10
H	5.57	5.46

2,2'-Dimethoxy 5,5'-diaceto para amino azo benzene—A suspension of the diazoamino compound in water was prepared and an equivalent quantity of HCl was added to it. The mixture was allowed to stand at room temperature for three days. The products were mostly of a tarry nature but a small quantity of aminoazo compound was recovered. It is an extremely feeble base, insoluble in ten-molar HCl but soluble in thirteen-molar HCl with a greenish blue color. Readily soluble in cold, and extremely soluble in hot, alcohol. Fine, submicroscopic dark-red crystals from fifty per cent alcohol; m. p., 198–200° corr., yield, very poor.

Analysis: $C_{18}H_{19}O_4N_3$	Calc.	Found
C	63.34	63.18
H	5.57	5.44

1-Methoxy 2-paranitrobenzalimino 4-acetophenone—Prepared by mixing 1-methoxy 2-amino 4-acetophenone with an equivalent quantity of para-nitro benzaldehyde and holding at 110° for fifteen hours.

This substance, although a solid at ordinary temperatures, is not a crystalloid, but a supercooled liquid. It is hard and very brittle at room temperature, softens above 135° and is entirely melted at 160° C. In color it ranges from deep red to yellow, depending upon the degree of subdivision. It is purified by dissolving in boiling alcohol, in which it is but moderately soluble. On cooling, it is precipitated in small droplets which soon become solid.

The above named amine was condensed with benzaldehyde and a compound obtained which was sirupy and solidified only on long standing. When warmed slightly, it reverted to the sirupy form. In an effort to obtain a Schiff's base which was a genuine crystalloid, para-nitro benzaldehyde was employed, with the above results.

Analysis: $C_{16}H_{14}O_4N_2$	Calc.	Found
C	64.43	64.18
H	4.70	4.69

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VITA

Leo P. Curtin was born on January 16, 1887, in Antrim, Pennsylvania, U. S. A., where he attended the local grammar school. At the age of fourteen, he commenced work in the coal mines of the Magee and Ellsworth Coal Company. A year later, he entered the employ of the Buffalo and Susquehanna Railroad as telegraph operator. During the following three years, he worked as telegraph operator, station agent and yardmaster for the Pennsylvania and the New York Central Railroads.

After serving for a brief time as travelling salesman for the Mt. Holly Stationery and Printing Company, Mt. Holly Springs, Penna., and then in various capacities in the stock brokerage business in Pittsburgh, he was employed as clerk for the Carnegie Steel Company at Sharon, Penna., and, later, as telegraph operator for the Standard Oil Company, in Pittsburgh. In 1908 he wrote life insurance in Pittsburgh for the Mutual Life Insurance Company, subsequently coming to New York to do clerical work in the actuary's office of the same company.

In September, 1909, he entered the employ of the Western Union Telegraph Company in New York, working first as telegraph operator, then traffic supervisor, then assistant repeater chief, then assistant wire chief.

On January first, 1917, he was appointed Night Wire Chief in the New York Main office, with supervision over the handling and testing of wires and related activities. This position he has held continuously up to the present.

He entered Columbia College in February, 1917, graduating in October, 1920, with the degree of Bachelor of Arts. In February, 1922, he was awarded the degree of Master of Arts by Columbia University.

He is a member of the American Chemical Society and has been elected to the Columbia chapters of the following honorary societies: Phi Beta Kappa, Phi Lambda Upsilon, Sigma Xi. In 1921-1922, he was University Scholar in Chemistry.

